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Review

Duration of untreated psychosis and negative symptoms – A systematic review and meta-analysis of individual patient data

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ABSTRACT

Background: Longer duration of untreated psychosis (DUP) is associated with poorer outcome in terms of positive symptoms, relapse rate, and time to remission. In contrast, the association with negative symptoms is less consistent.

Aims: The study had three aims. First, to arrive at a more precise estimate of the correlation between DUP and negative symptoms than previous reviews, by substantially increasing the amount of available data. Second, to see whether the strength of this correlation attenuated over longer follow-up intervals. Third, to determine whether there is a relationship between DUP and changes in negative symptoms.

Method: Relevant databases were searched for studies published between December 1992 and March 2009 that reported data on DUP and negative symptoms. We obtained individual patient data where possible and calculated summary correlations between DUP and negative symptoms for each study at baseline, short and long-term follow-up. We used multilevel regression analysis to examine whether the effect of DUP on negative symptoms was the greatest in the early stages of illness.

Results: We included 28 non-overlapping studies from the 402 papers detected by the search strategy. After contacting the authors we obtained individual patient data from 16 of these studies involving 3339 participants. The mean DUP was 61.4 weeks (SD = 132.7, median DUP = 12.0). Shorter DUP was significantly associated with less severe negative symptoms at baseline and also at short (1–2 years) and longer term follow-up (5–8 years) ($r = 0.117, 0.180$ and 0.202 respectively, $p < 0.001$). The relationship between improvement in negative symptoms and DUP was found to be non-linear: people with a DUP shorter than 9 months showed substantially greater negative symptom reduction than those with a DUP of greater than 9 months.

Conclusions: Shorter DUP is associated with less severe negative symptoms at short and long-term follow up, especially when the DUP is less than 9 months. Since there is no effective treatment for negative symptoms, reducing DUP to less than 9 months may be the best way to ameliorate them.

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1. Introduction

Negative symptoms are a core component of the schizophrenia syndrome and are commonly described in terms of five dimensions: blunted affect, alogia, anhedonia, avolition and asociality (Blanchard

et al., 2005; Kirkpatrick et al., 2006; Mäkinen et al., 2008). Negative symptoms are associated with poor functional outcome (Malla et al., 2004), cognitive deficits (Heydebrand et al., 2004), social dysfunction and poor quality of life (Addington and Addington, 1993; Schmitz et al., 2007; Petersen et al., 2008). Negative symptoms are common: the prevalence in short-term follow-up studies (up to 2.5 years) is about 45% (Pogue-Geile and Harrow, 1985; Malla et al., 2002, 2004), and in longer term studies (7.5–10 years) 20–30% (Herbener and Harrow, 2001).

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There is no established treatment for primary negative symptoms (Kirkpatrick et al., 2006; Buckley and Stahl, 2007). Pharmacological treatments, such as antipsychotics have only a marginal impact on negative symptom severity (Leucht et al., 2011). Some psychosocial treatment trials have shown an effect on negative symptoms. Cognitive behavioral therapy showed a positive effect on negative symptoms up to 24 months of follow-up (NICE, 2010). In addition there have been three small but promising trials on peer support groups (Castelein et al., 2008), music therapy (Gold et al., 2009) and body oriented psychosocial therapy (Rohricht and Priebe, 2006).

Pending replication of these studies, it may be that the best way to deal with negative symptoms apart from cognitive therapy is prevention. Many countries have already adopted an early intervention approach to the treatment of psychosis on the basis that there is a robust association between duration of untreated psychosis and the long-term severity of positive symptoms. A similar association between negative symptoms and outcome would support early intervention for negative symptoms (Melle et al., 2008).

So far two meta-analyses have examined the correlation between DUP and negative symptoms (Marshall et al., 2005; Melle et al., 2008). The first by Marshall et al. reported an association at 6 and 12 months but not at baseline and 24 months (Marshall et al., 2005). The second by Perkins et al. claimed that patients with shorter DUP experienced less negative symptoms at baseline and follow-up (Perkins, 2006). While making a valuable contribution, both reviews share three limitations. First, neither study provided a precise analysis of the effect of DUP at long term follow-up, thus Marshall et al. did not consider data on negative symptoms beyond 24 months and Perkins et al. summarized data of all follow-up assessments varying from 3 months to 15 years into one combined effect size. Second, both studies relied exclusively on published data, which meant that they excluded a substantial number of studies that collected pertinent data but did not publish it in a format that could be used in their analyses. Third, both studies used combined correlation coefficients calculated by different techniques, for example parametric in some studies and non-parametric in others.

As a consequence of these limitations, neither study was able to consider the relationship over time i.e. the linearity of the relationship between DUP and negative symptoms. So far most studies did focus on the relationship between DUP and positive symptoms (Drake et al., 2000). Not only a positive association was found in most studies but also a non-linearity of this relationship between DUP and positive symptoms. This means that in a patient with a DUP of less than 12 months, the effect of a DUP reduction of for example 2 months on positive symptoms would be greater than a two month reduction in someone with a DUP of more than 12 months. It is possible therefore that a similar non-linear relationship might exist with negative symptoms, with important clinical implications.

The present study therefore had three aims: (a) to provide a precise estimate of the correlation between DUP and negative symptoms by substantially increasing the amount of available data contributing to the analysis; (b) to see if the strength of any correlation attenuates at longer follow up intervals; (c) to determine whether the relationship between DUP and negative symptoms was non-linear.

2. Methods

2.1. Search strategy

The search aimed to detect all cohort studies that had examined DUP and negative symptoms in first episode psychotic patients, and were available for review up to March 2009. The search included

the databases MEDLINE and PUBMED using the keywords “DUP” AND “psychosis” OR “schizophrenia” and the combination “duration” AND “untreated” AND “psychosis” OR “schizophrenia”. In addition references cited in these papers were examined.

2.2. Inclusion criteria and data extraction

Studies were included if they met two criteria. First, participants had experienced a first episode of psychosis defined as: schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder or psychosis NOS, according to either the Diagnostic Statistical Manual (DSM-IV) or the International Classification of Diseases (ICD-10) classification systems. Second, DUP and negative symptoms had been measured using a standardized method (which for negative symptoms was one of the three commonly used scales in this area), i.e.: the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989), or the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). We included all follow-up studies regardless of research design.

Abstracts were screened independently by two reviewers (N.B. and R.K.), and copies were obtained of any papers describing potentially eligible studies. Each paper was assessed independently by two reviewers and any disagreements resolved by discussion with a third reviewer (L.W.) (for table of included studies see Appendix 1). To overcome the limitations of previous meta-analyses it was necessary to obtain a substantial dataset of individual patient data (IPD) from first-episode studies (Stewart and Parmar, 1993; Stewart and Tierney, 2002). The authors of included studies were contacted and asked to provide anonymized individual patient data on: gender, age at onset, DUP, and negative symptom scores at baseline and all available follow-up points.

2.3. Analysis

We calculated the correlation between DUP and negative symptoms for short and long term follow up. We defined short-term follow up as between 12 and 24 months and long term follow up as 60 to 96 months. Studies of which a Spearman correlation was published were used for sensitivity analysis.

In cases where more than one assessment was available for short or long term follow up, we used the first assessment. The data were analyzed using a two-step approach. First, individual patient data from each study were analyzed using the non-parametric Spearman's Rank Correlation. We choose a non-parametric test because of the significant positive skew in the distribution of DUP. In the second step, a meta-analysis of the aggregated data produced for each study was performed using Comprehensive Meta-Analysis in order to summarize the correlations (CMA, version 2005, Biostat, Inc., Englewood, NJ, 2005) (Borenstein et al., 2009). We used random effect models because of great differences between research designs. Correlation data were synthesized with Fisher's z transformation into a single correlation coefficient (r) with 95% confidence intervals (CI).

CMA also tests for the heterogeneity of the sample populations using I^2 , a test parameter, which evaluates the null hypothesis that all studies are assessing the same effect size. I^2 indicates the percentage of total variation across studies due to heterogeneity rather than chance, and ranges from 0% (no heterogeneity) to 100% (high heterogeneity). Values for I^2 of 25%, 50% and 75% are considered to represent low, moderate and high heterogeneity respectively (Higgins et al., 2003).

A major concern when conducting a meta-analysis is publication bias: studies that report relatively large effect sizes are more likely to be published than studies with smaller effect sizes. If the included studies are a

biased sample of all relevant studies, consequently the bias will be reflected in the mean effect computed by the meta-analysis. A funnel plot can be made to examine the publication bias using Comprehensive Meta-Analysis (CMA, version 2005, Biostat, Inc., Englewood, NJ, 2005).

We examined the linearity of the relationship between DUP and negative symptom change using the method developed by Drake (Drake et al., 2000). We used a multilevel regression analysis (XTREG in STATA release 11.0) (Snijders and BRJ, 1999; StataCorp., 2009) to estimate the magnitude of the effect of DUP on negative symptom severity reduction after various periods of follow-up with the individuals nested within each study. Subsequently, explanatory variables (gender and age at onset) were added, as potential confounders. The skewed distribution of DUP was corrected by converting DUP to its logarithm (logDUP) thus allowing the use of parametric statistics. The change of negative symptoms from baseline to follow-up was calculated as a percentage of baseline negative symptom severity and added in the multilevel regression analysis as the dependent variable. We conducted the analysis for negative symptom change at short and long-term follow up, as defined above.

3. Results

3.1. Studies and patients

A total of 402 papers were identified by the search strategy, from which we identified 28 non-overlapping first episode

studies that met inclusion criteria (see Appendix 1) (Montague et al., 1989; Barnes et al., 2000; Craig et al., 2000; de Haan et al., 2000; Drake et al., 2000; Ho et al., 2000; Larsen et al., 2000; Black et al., 2001; Verdoux et al., 2001; Cullberg et al., 2002; Malla et al., 2003; Addington et al., 2004; Sim et al., 2004; Chen et al., 2005; Harris et al., 2005; Manchanda et al., 2005; Melle et al., 2005; Oosthuizen et al., 2005; Petersen et al., 2005; Wade et al., 2005; Clarke et al., 2006; Uçok et al., 2006; Wunderink et al., 2006; Crespo-Facorro et al., 2007; Malla et al., 2007; Vyas et al., 2007; Gorna et al., 2008; Yamazawa et al., 2008). The selected studies included a total of 3998 participants. Following written requests, authors of 16 studies submitted their data sets that covered a total of 3339 participants. From the 12 studies of which individual patient data were not available, 2 studies reported a Spearman correlation at short term follow-up (1–2 years). Table 1 shows the distribution of DUP, gender and age at onset of participants of whom individual patient data were available at baseline. The follow-up data of 2 studies were incomplete and therefore only baseline data were used in our analysis (Montague et al., 1989; Malla et al., 2003; Melle et al., 2004; Manchanda et al., 2005; Malla et al., 2007).

The mean age at onset of participants was 26.0 years (SD = 8.9), and the mean DUP was 61.4 weeks (SD = 132.7 weeks, median DUP = 12.0 weeks). 59% of the participants at baseline were males.

Table 1
Summary of the 16 included first episode studies.

Study inclusion period	N baseline	Gender		Age at onset (SD)		Mean DUP in weeks (SD)	Median DUP in weeks	N at short term follow-up (12–24 months)	N at long term follow-up (60–96 months)
		M	F	M	F				
Addington (Addington et al., 2004) (Jan. 1997–Dec. 2000)	240	161	79	23.4 (6.7)	26.4 (10.3)	77.1 (134.0)	26.0	199	50
Barnes (Barnes et al., 2000) (Feb 1995–Oct 2001)	98	75	23	23.5 (6.6)	27.2 (8.3)	54.0 (88.1)	20.0	96	–
Chen (Chen et al., 2005) (Sept. 1997–March 2000)	93	42	51	29.0 (9.2)	33.0 (9.7)	44.4 (135.7)	25.7	93	–
Clarke (Clarke et al., 2006) (Febr. 1995–Febr. 1999)	152	96	56	27.8 (6.4)	26.6 (8.3)	71.0 (115.9)	23.6	–	94
Craig (Craig et al., 2000) (1989–1995)	354	194	160	28.6 (15.8)	30.3 (11.9)	66.4 (186.2)	3.6	258	–
Cullberg (Cullberg et al., 2002) (Jan. 1996–Dec. 1997)	175	97	78	25.3 (6.4)	29.4 (7.1)	66.4 (163.2)	3.6	–	122
Drake (Drake et al., 2000) (July 1996–aug. 1998)	255	176	79	28.0 (9.9)	32.2 (10.7)	38.7 (82.2)	12.0	182	–
Gorna (Gorna et al., 2008) (1988–2002)	86	34	52	26.6 (7.0)	23.6 (4.6)	40.4 (57.0)	12.9	83	74
Harris (Harris et al., 2005) (March 1989–July 1997)	318	216	102	21.7 (4.1)	23.9 (5.2)	24.1 (50.1)	5.8	295	135
Malla (Malla et al., 2007) (January 1997–July 2003)	153	116	37	22.8 (7.2)	28.9 (12.0)	70.9 (110.3)	23.9	–	–
Manchanda (Manchanda et al., 2005) (May 1996–Dec. 2001)	122	93	29	22.1 (6.3)	28.8 (11.2)	70.7 (120.6)	21.6	122	–
Melle (Melle et al., 2004) (Jan. 1997–Dec. 2000)	301	176	125	25.1 (7.9)	29.4 (11.2)	47.4 (117.7)	9.0	271	–
Montague (Montague et al., 1989) (1986–1988)	109	51	58	26.7 (6.8)	28.1 (8.3)	28.9 (88.1)	20.0	–	–
Petersen (Petersen et al., 2005) (Jan. 1998–Dec. 2000)	578	235	343	24.3 (6.6)	24.5 (6.1)	106.0 (177.2)	34.4	394	247
Uçok (Uçok et al., 2006) (> 1996)	148	84	64	23.3 (6.2)	25.6 (9.3)	32.8 (39.5)	17.1	54	–
Wunderink (Wunderink et al., 2006) (Okt. 2001–Dec. 2002)	157	113	44	25.6 (6.0)	28.8 (7.2)	46.0 (111.6)	4.4	120	105
Overall	3339	1959	1380	25.0 (8.6)	27.3 (9.2)	M 61.0 (125.5) F 61.9 (142.4)	13.3	1268 899	458 369

M = male.

F = female.

4. Association between duration of untreated psychosis and negative symptoms

Fig. 1 shows a summary of the correlations between DUP and negative symptoms at baseline and short (1–2 years) and long-term follow-up (5–8 years). The data show a statistically significant positive correlation between DUP and negative symptoms at baseline (Fisher's $z=0.117$, 95%CI 0.064–0.17), at short-term follow-up (Fisher's $z=0.18$, 95%CI 0.086–0.274) and at long-term follow-up (Fisher's $z=0.202$, 95%CI 0.137–0.267). There is no evidence for attenuation in the strength of the association with longer follow up. Tests for heterogeneity showed that the studies were low to moderately heterogeneous ($I^2=48\%$ at baseline, 75.9% at short term, 27.3% at long term follow-up). A sensitivity analysis was done by adding the reported Spearman correlations to the meta-analysis at short term follow-up from the two studies of which individual patient data were not obtained (Sim et al., 2004; Oosthuizen et al., 2005; Subramaniam et al., 2007). These two additional

studies did not substantially alter the reported correlations of heterogeneity statistics ($I^2=71.8\%$).

5. Predicted negative symptom change

2150 patients nested in 12 studies were included in the multilevel analysis to explore the effect of DUP on negative symptom reduction at short-term follow-up. The mean follow-up assessment was 15.5 months (95%CI 15.3–15.7). In the multilevel analysis for long-term follow-up, 795 individuals nested in 7 studies were included and the mean follow-up assessment was 71.4 months (95%CI 70.2–72.7).

Figs. 2 and 3 show the percentage change in negative symptoms predicted by a given DUP at short and long-term follow-up respectively.

6. Discussion

The analysis showed that there is a significant positive association between DUP and negative symptoms at: baseline, short

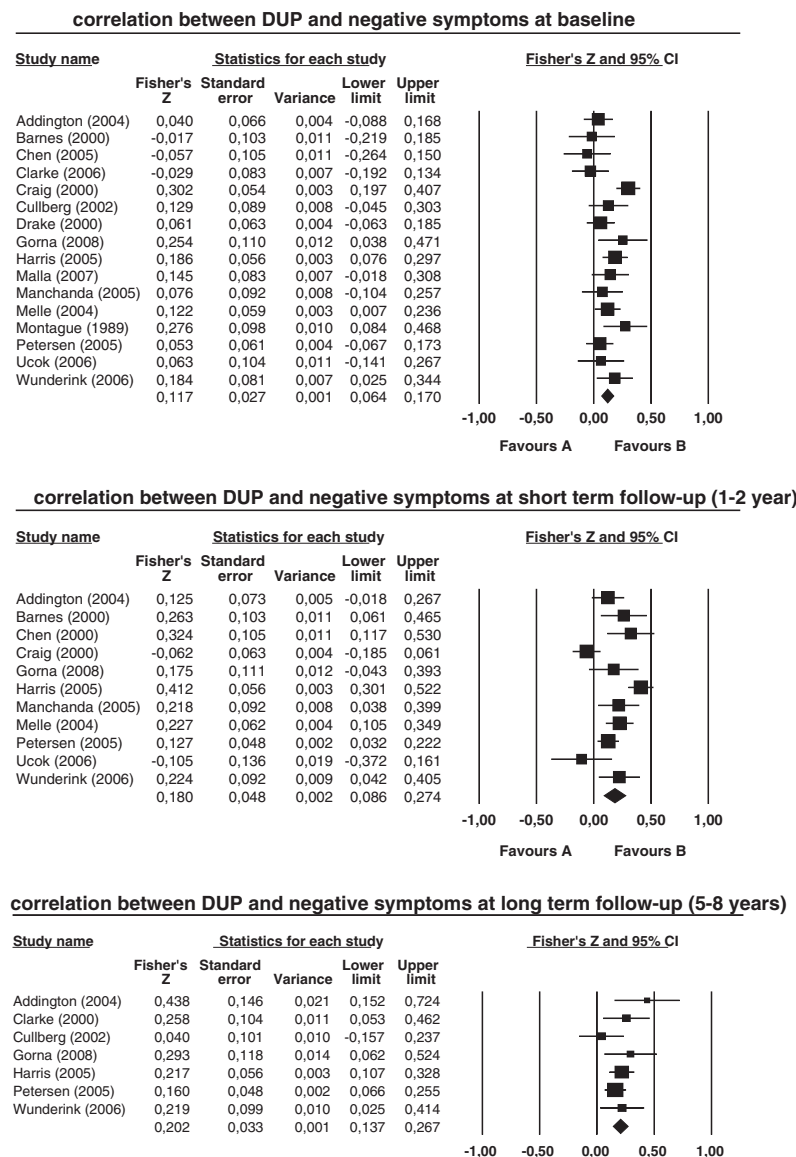


Fig. 1. Correlations between DUP and negative symptoms at baseline, after 1-2 years follow-up and after 5-8 years follow-up.

(1–2 years) and long-term (5–8 years) follow-up. The effect is non-linear: negative symptoms and DUP are positively associated if DUP was less than 9 months. For those patients with a DUP longer than 9 months negative symptoms are not associated linearly. A reduction in DUP in someone with a shorter DUP (i.e. less than 9 months) might therefore have a greater impact on negative symptoms than the same reduction in someone with a DUP greater than nine months. These findings are in accordance with the findings of the TIPS study and the study of Malla et al. (2002, 2004), both of which suggested that reduction of DUP may be as important for improving the severity of negative symptoms as it is for positive symptoms (Melle et al., 2008). Our finding of a non-linear association between DUP and negative symptoms is similar to that reported by Drake et al. for total PANSS scores (Drake et al., 2000) albeit in a small sample with a short follow-up.

The association between a longer DUP and persistence of negative symptoms (after 1–2 years) is consistent with the hypothesis that in many cases psychosis is a clinical manifestation of a progressive pathological process in which early detection and intervention could be effective in ameliorating the course of the disorder. Figs. 2 and 3 suggest the existence of a critical period of DUP of about 9 months in which the association with negative symptoms is particularly strong. This finding supports arguments for early detection and intervention programs, since apart from prevention, there is no evidence-based treatment for negative symptoms (Melle et al., 2008). However, it is important to emphasize that this analysis does not prove that there is a causal association between DUP and negative symptoms.

An important strength of this study is the use of individual patient data (IPD). The use of IPD in meta-analyses (Stewart and Parmar, 1993; Stewart and Tierney, 2002) offers a greater resolution of effect size than meta-analyses based on study level data. Individual patient data permitted us to reanalyze all the data using the same method of correlation and to calculate correlations that had not been previously published. We were also able to combine data across studies to explore the relationship between DUP and negative symptoms.

As a result of obtaining individual patient data, this review has substantially increased the amount of information available for analysis. Consequently, it has extended the findings of previous meta-analyses by providing more precise estimates of the correlation between duration of untreated psychosis and negative symptoms, examining the correlation at both short and long-term follow up and exploring the linearity of the association. This is of clinical importance because the window of opportunity to intervene to improve the prognosis of psychosis is considered to last 3–5 years (Birchwood, 2000).

The main limitation of the review is that data were obtained on only 16 of 28 eligible studies. The 12 studies not obtained included

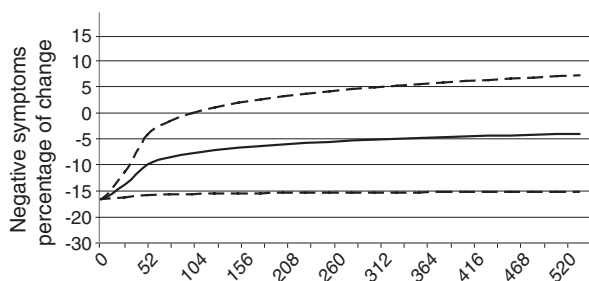


Fig. 2. Predicted change in negative symptoms after short term, follow-up (1–2 years) against duration of untreated psychosis in weeks (with 95% CIs).

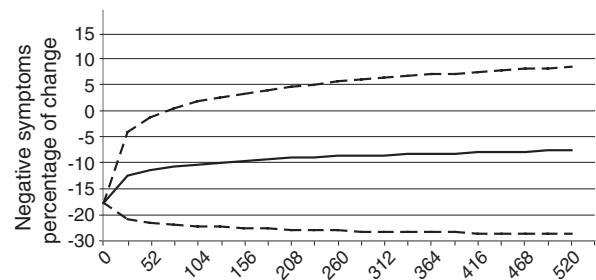


Fig. 3. Predicted change in negative symptoms after longer term, follow-up (5–8 years) against duration of untreated psychosis in weeks (with 95% CIs).

659 patients. Three studies reported correlations between DUP and negative symptoms at 12 to 24 months of follow-up of which 2 were Spearman correlations. Adding data of these two studies in the meta-analysis did not substantially alter the reported correlations of heterogeneity statistics. We were not able to correct for possible confounding variables on the correlation between DUP and negative symptoms, such as drug use or premorbid adjustment because we did not have access to these data.

Previous studies have noted considerable variation in first episode psychosis cohorts (Schmitz et al., 2007), for example in: participant characteristics; instruments to assess symptoms; measures of DUP; and definitions of DUP. In this meta-analysis we included observational studies as well as interventional studies. No interventional studies targeting negative symptoms were included. Some studies rely entirely on the patients' own reports and thus reflect the onset of the subjective experiences of psychosis while most studies have validated ratings of DUP by including interviews with family members, hospital records and reviews after one year of follow-up. Despite these problems, this analysis detected only a mild to moderate degree of statistical heterogeneity between studies, at a level that was not sufficient to undermine the main findings. We conducted a funnel plot in order to test publication bias. The plot shows the presence of symmetry for all analysis. Since the sampling error is random, this underpins the idea that there is no substantial publication bias.

In summary, the relationship between DUP and negative symptoms has been underestimated, and is in fact strong and persistent. A DUP of less than 9 months appears to be a strong predictor of improvement of negative symptoms, while most patients with a DUP longer than 9 months show persistent negative symptoms. It is unknown to what extent reducing DUP will improve outcome. However efforts to shorten DUP might decrease negative symptom severity as has been done in the Scandinavian TIPS study (Melle et al., 2008). The absence of substantially effective treatments for negative symptoms supports preventive interventions with the potential to ameliorate negative symptoms, e.g. by reducing DUP.

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There was no funding for this study.

Contributors

Nynke Boonstra designed the study and wrote the protocol together with Rianne Klaassen and Lex Wunderink. Together they performed the literature searches and analysis. Max Marshall supported the analysis and interpretation, and Sjoerd Sytema, Lieuwe de Haan and Durk Wiersma read and revised the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Appendix 1. Description of included cohorts

Cohort	Cohort size	Country	Age of population in years	Length of follow up (months)	Symptom scale	DUP definition	Instrument used to determine DUP
Addington et al. (2004)	240	Canada	–	36	PANSS	From the time the individual first described the onset of any positive sx that could be rated as 4 or more on the PANSS until the first effective treatment was initiated.	IRAOS
Barnes et al. (2000) and Subramaniam et al. (2007)	98	United Kingdom	16–55	12	SANS	Onset of psychotic sx to first treatment with antipsychotic medication.	NS
Black et al. (2001)	21	Canada	–	6	PANSS	Onset of positive psychotic sx (score of ≥ 4 on any of the positive subscale items in the PANSS, these sx must have lasted throughout the day for several days or appeared several times a week) until the beginning of treatment with antipsychotic medication.	IRAOS
Chen et al. (2005)	93	Hong Kong	18–55	36	PANSS	Onset date for the earliest psychotic sx.	IRAOS
Clarke et al. (2006)	152	Ireland	12>	96	PANSS	First noted psychotic symptoms to presentation to the psychiatric services for initiation of adequate treatment of a psychotic illness.	SCID
Craig et al. (2000)	354	United States	15–60	24	SANS	Occurrence of the first clear psychotic symptom to first psychiatric hospitalization.	SCID
Crespo-Facorro et al. (2007)	61	Spain	15–60	36	SANS	First continuous (present most of the time) psychotic symptoms to initiation of adequate antipsychotic drug treatment.	SCID
Birchwood (2000) and Cullberg et al. (2002)	175	Sweden	18–45	60	BPRS	First psychotic sx until the first contact with psychiatric services.	SCID
de Haan et al. (2000) (61)	88	The Netherlands	Adolescents	72	PANSS	First onset of psychotic sx until start of antipsychotic medication (for a minimum of 6 weeks).	NS
Drake et al. (2000)	255	United Kingdom	16–64	18	PANSS	Onset of delusions and hallucinations.	NS
Gorna et al. (2008)	86	Poland	Adults	60	PANSS	Onset of first psychotic symptoms to the initiation of antipsychotic treatment	ICD 10
Harris et al. (2005)	318	Australia	16–45	96	SANS	Onset of psychosis to initiation of treatment.	RPMIP
Ho et al. (2000)	74	United States	–	6	SANS	Onset of first sx to the initiation of neuroleptic treatment	CASH + PSYCH-base
Larsen et al. (2000)	43	Norway	15–55	12	PANSS	Onset of psychotic sx to hospitalization for psychosis or initiation of adequate treatment.	SCID
Malla et al. (2007)	172	Canada	16–50	12	PANSS	Onset of psychotic sx to the time of initiation of continuous antipsychotic treatment, plus any periods of psychosis previously experienced and spontaneously remitted.	CORS
Malla et al. (2003)	153	Canada	16–50	36	SANS,	Initial onset of psychosis to treatment (antipsychotic medication of a dosage that should actually lead to a significant response in most patients for a period of time (4 weeks)).	SCID
Manchanda et al. (2005)	122	Canada	16–50	24	SANS	Onset of clear symptoms of psychosis to the initiation of antipsychotic medications.	CORS
Melle et al. (2005)	301	Scandinavia	18–65	24	PANSS	Onset of psychosis (first week with sx corresponding to a PANSS score of ≥ 4 or on positive subscale items 1, 3, 5 or 6 or on the general subscale item 9) until start of adequate treatment (structured treatment with antipsychotic medications or hospitalization in a highly staffed psychiatric ward to manage psychotic sx.).	SCID
Montague et al. (1989)	109	United Kingdom	16–50	120	SANS	First onset of positive symptoms to index admission	PSE-9
Oosthuizen et al. (2005)	57	South Africa	16–55	24	PANSS	Onset of overt hallucinations or delusions, up to the initiation of treatment with antipsychotic medication.	SCID
Petersen et al. (2005)	578	Scandinavia	18–45	24	SANS	Appearance of at least one psychotic sx until initiation of adequate treatment	SCAN & IRAOS.
Sim et al. (2004)	278	Singapore	18–40	24	PANSS	Onset of psychotic sx and the time that treatment was initiated.	SCID-P
Uçok et al. (2006)	148	Turkey	15–45	12	SANS	Onset of the first positive sx to the first hospitalization.	SCID e.
Verdoux et al. (2001)	65	France	<60	24	PANSS	Onset of positive symptoms to first admission.	MINI
Vyas et al. (2007)	40	United Kingdom	Adolescents	48	PANSS	Age of onset of psychosis tp age at initiation of antipsychotic treatment.	SCID/KID-SCID
Wade et al. (2005)	126	Australia	15–30	15	SANS	Onset of psychotic symptoms to service entry.	RPMIP

Appendix 1 (continued)

Cohort	Cohort size	Country	Age of population in years	Length of follow up (months)	Symptom scale	DUP definition	Instrument used to determine DUP
Wunderink et al. (2006)	157	The Netherlands	18–45	24	PANSS	First manifestation of any positive psychotic sx to the start of antipsychotic treatment.	SCAN
Yamazawa et al. (2008)	34	Japan	16–44	12	PANSS	Onset of psychotic symptoms to the first prescription of neuroleptics for psychotic symptoms and the first prescription of neuroleptics for psychosis	NS

CASH; Comprehensive Assessment of Psychiatric History.

CORS; Course of Onset and Relapse Schedule.

IRAOS; Interview for the Retrospective Assessment of the Onset of Schizophrenia.

MINI; Mini International Neuropsychiatric Interview.

PANSS; Positive and Negative Syndrome Scale.

PSE; Present State Examination.

RPMIP; Royal Park Multidiagnostic Instrument for Psychosis.

SANS; Structured Assessment of Negative Symptoms.

SAPS; Structured Assessment of Positive Symptoms.

SCID; Structured Clinical Interview for DSM disorders.

SCAN; Schedules for Clinical Assessment in Neuropsychiatry.

ICD-10; International Statistical Classification of Diseases.

NS; not specified.

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